AJNR

Peripheral Third Cranial Nerve Enhancement in Multiple Sclerosis

M. Tariq Bhatti, Ilona M. Schmalfuss, Lorna S. Williams and Ronald G. Quisling

AJNR Am J Neuroradiol 2003, 24 (7) 1390-1395
http://www.ajnr.org/content/24/7/1390

AJNR Am J Neuroradiol 24:1390–1395, August 2003

Case Report

Peripheral Third Cranial Nerve Enhancement in Multiple Sclerosis

M. Tariq Bhatti, Ilona M. Schmalfuss, Lorna S. Williams, and Ronald G. Quisling

Summary: Cranial nerve III dysfunction in multiple sclerosis (MS) is uncommon. Seven cases of isolated cranial nerve III paresis associated with MS have been reported in the English-language literature. MR imaging was obtained in five cases demonstrating lesions within the midbrain. We present the detailed clinical and MR imaging findings of a young woman with MS and an isolated, painful pupil involving complete left cranial nerve III palsy. Initial MR imaging showed isolated enhancement of the cisternal portion of the cranial nerve III, suggesting that peripheral nervous system involvement may develop as part of the disease process in some patients with MS.

Multiple sclerosis (MS) has traditionally been thought of as a chronic, autoimmune, inflammatory, demyelinating disease of the central nervous system (CNS) (1). Despite our expanding knowledge of the disease process, MS remains difficult to understand because of its clinical, immunopathologic, radiologic, and genetic heterogeneity (2). Furthermore, etiology and immunopathomechanic explanations of MS remain elusive (3). Although MS is considered a disease of the CNS, several studies have demonstrated peripheral nervous system (PNS) involvement in a subgroup of patients, suggesting a continuum of a disease spectrum between traditionally classified demyelinating disorders of the PNS and CNS (4–7). We report the unique case of a young woman with MS and a painful pupil, involving complete cranial nerve III palsy associated with abnormal enhancement of the cisternal portion of the nerve. In a subgroup of patients, MS can affect the PNS and possibly represents either a distinct disease or a variant of MS with clinical, radiologic, and immunopathologic features characterized by the targeted antigen.

Case Report

In February 1998, a 30-year-old white woman was evaluated by a neurologist for complaints of numbness with deep-dull pain of the left upper and lower extremities, Lhermitte's sign, and a heightened sensitivity to touch of the left side of the body. MR imaging revealed a lesion within the cervical spinal cord. Findings in the brain were normal. Weekly interferon β-1a was initiated for presumed MS. Treatment was discontinued after 6 months because of the patient's severe depression. Upon reevaluation by a second neurologist, the diagnosis of MS was dismissed.

In April 2001, she presented with binocular diplopia of 1-day duration associated with pain over the left eyebrow. The morning of presentation, she noticed her left pupil was slightly larger than the right. On clinical examination, the visual acuity was 20/20 in both eyes. The left pupil measured 1 mm larger than the right and left upper eyelid ptosis of 1 mm was noted. Extraocular movements appeared full in both eyes with a small (two prism diopter) vertical misalignment of the eyes in primary gaze. Findings of slit-lamp biomicroscopy, intraocular pressures, visual field testing, and dilated fundus examination were all normal. The cranial nerve and neurologic examination were otherwise normal. Findings of cranial MR imaging and angiography with gadolinium were interpreted as normal. Three days later, there was 4 mm of left upper eyelid ptosis, the left pupil was 3 mm larger than the right, and there was limitation of elevation, depression, and adduction of the left eye. A compressive pupil involving cranial nerve III palsy was suspected. Findings at cerebral angiography were negative. CSF analysis revealed a white blood cell count of 3 cu/mm, red blood cell count of 10 cu/mm, protein 43 mg/dL (normal range 12–60 mg/dL), glucose 59 mg/dL (normal range 40–70 mg/dL), albumin 37.5 mg/dL, IgG 4.4 mg/dL, and myelin basic protein 2.0 μg/L (normal range 0.0–4 μg/L). Oligoclonal bands were absent. Findings of CSF cytology and cultures were negative. Complete blood count and metabolic profile were normal. Westergren sedimentation rate was 11 mm/h. Antinuclear antibodies were not detected. Serum angiotensin converting enzyme level and chest radiograph were normal. Prothrombin time, activated partial thromboplastin time, lupus anticoagulant, and anticardiolipin antibodies were all normal or negative. Serum antibody titers for *Borrelia burgdorferi*, *Treponema pallidum,* and *Bartonella henselae* were all negative. B_1, B_6, and B_{12} levels were normal.

One week later, there was complete left upper eyelid ptosis and an 8-mm fixed left pupil. The left eye was unable to elevate, depress, or adduct. A repeat cranial MR image demonstrated enhancement and thickening of the left cranial nerve III extending from its exit zone within the mesencephalon to the cavernous sinus (Fig 1). The T2-weighted images (not shown) showed focal area of high signal intensity in the left ventral mesencephalon just medial to the cerebral peduncle. MR findings of the cervical spine were normal. Retrospective review of the MR examination performed 1 week earlier demonstrated similar, but considerably less apparent, abnormalities (Fig 2).

Four weeks after receiving intravenous methylprednisolone (1 g/day for 3 days) the pupils were of equal size, and eye movements returned to normal. Follow-up cranial MR imaging 4 months later showed persistent subtle enhancement of the left cisternal portion of cranial nerve III.

The patient was doing well, until March 2002, when she began to experience Lhermitte's sign and numbness of the left hand and foot. Cranial MR demonstrated few hyperintense

Received November 11, 2002; accepted after revision, December 9.

From the Departments of Ophthalmology (M.T.B.), Neurology (M.T.B.), and Radiology (I.M.S., R.G.Q.), University of Florida College of Medicine, Gainesville, FL; and the Department of Radiology (L.S.W.), JFK Medical Center, Atlantis, FL

Supported in part by an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, NY.

Address correspondence to M. Tariq Bhatti, M.D., University of Florida College of Medicine, Department of Ophthalmology, Box 100284 JHMHSC, Gainesville, FL.

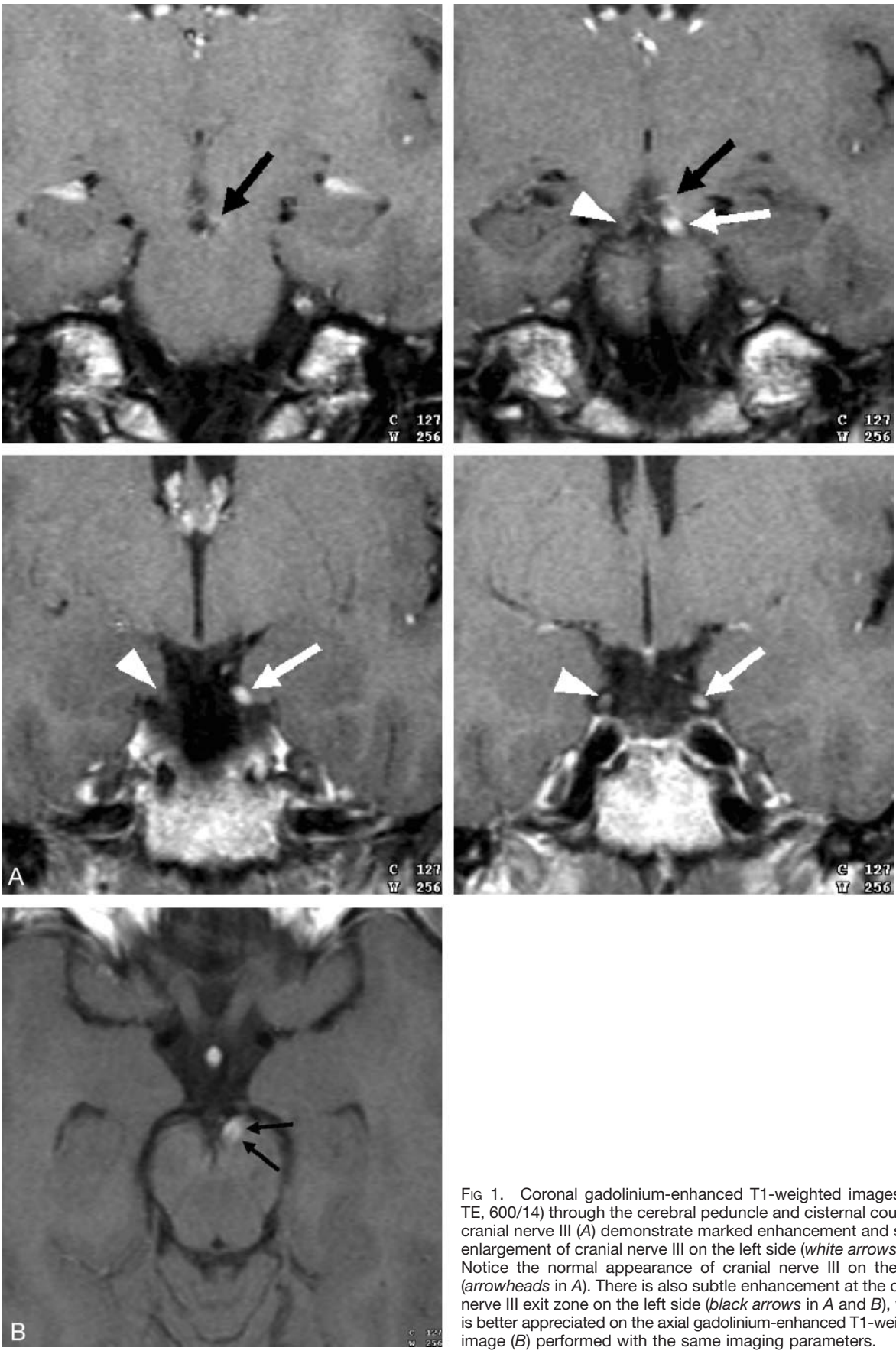
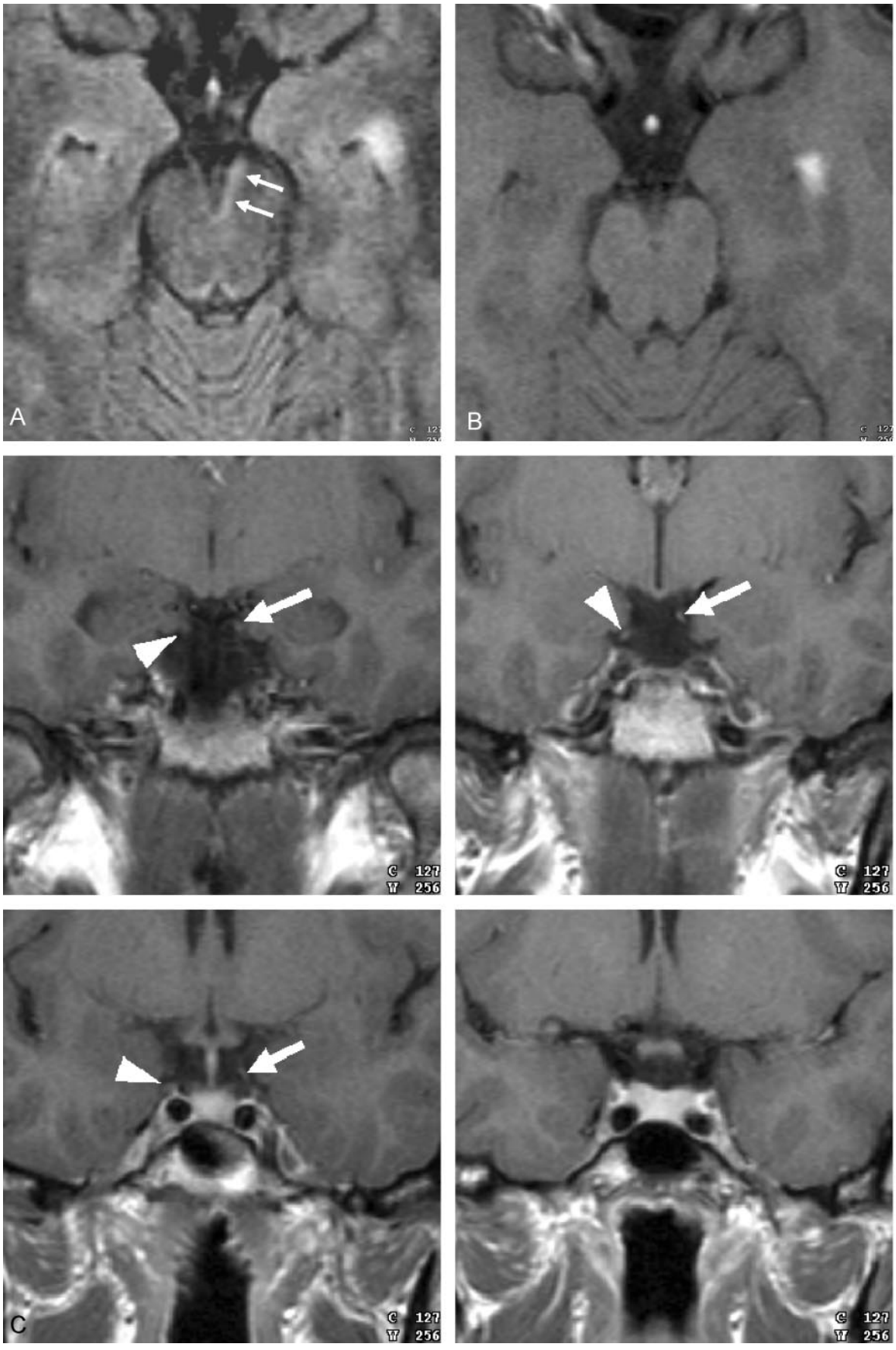


FIG 1. Coronal gadolinium-enhanced T1-weighted images (TR/TE, 600/14) through the cerebral peduncle and cisternal course of cranial nerve III (*A*) demonstrate marked enhancement and subtle enlargement of cranial nerve III on the left side (*white arrows* in *A*). Notice the normal appearance of cranial nerve III on the right (*arrowheads* in *A*). There is also subtle enhancement at the cranial nerve III exit zone on the left side (*black arrows* in *A* and *B*), which is better appreciated on the axial gadolinium-enhanced T1-weighted image (*B*) performed with the same imaging parameters.


A
B
C 127
W 256
C 127
W 256
C
C 127
W 256
C 127
W 256

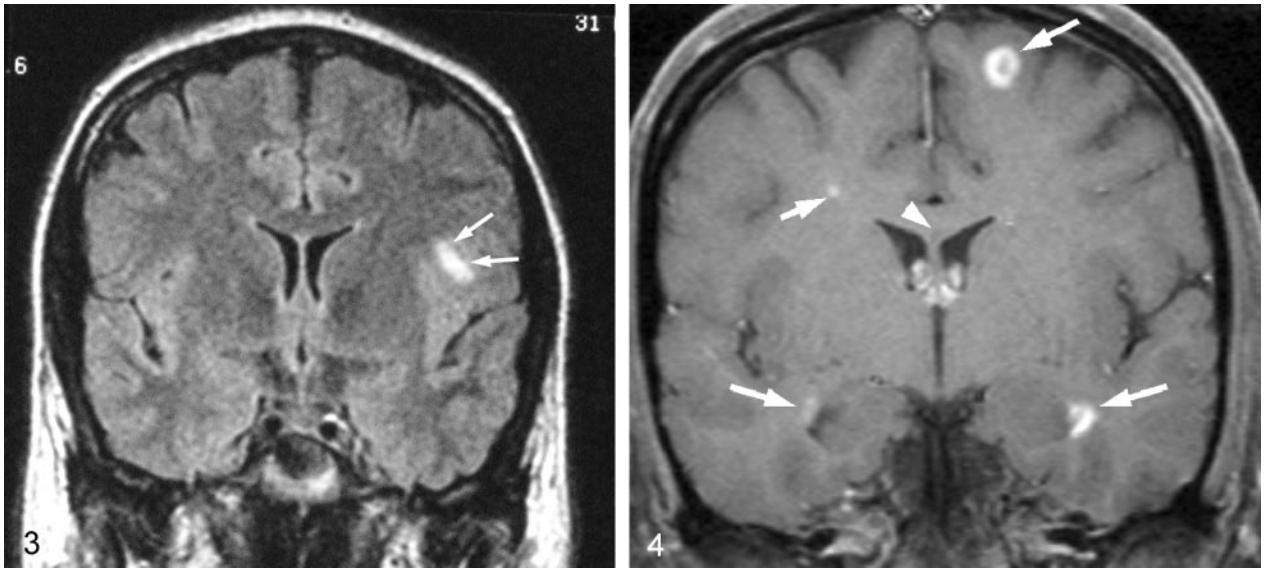


FIG 3. Coronal FLAIR-weighted image (TR/TE, 10,002/168) obtained at the level of the anterior horns of the lateral ventricles shows a focal area of increased signal intensity (*arrows*) in the subcortical white matter of the inferior frontal lobe on the left side.

FIG 4. Coronal gadolinium-enhanced T1-weighted image (TRTE, 882/14) obtained at the level of the anterior horns of the lateral ventricles shows multiple enhancing white matter lesions (*arrows*). There is also a nonenhancing lesion in the corpus callosum in midline (*arrowhead*).

T2-weighted lesions throughout the cerebral white matter, including the corpus collosum (Fig 3). T2-weighted spinal MR imaging revealed a hyperintense lesion within the dorsal aspect of the spinal cord extending from the C4–C5 to the C7 level. Following the administration of gadolinium the midportion of the spinal cord lesion and few of the cerebral lesions demonstrated enhancement. The diagnosis of MS was made, and the patient began treatment with glatiramer acetate.

Four months later, she developed decreased vision in the left eye and ocular pain associated with eye movements. Visual acuity was 20/400 with a left relative afferent pupillary defect. Cranial and orbital MR revealed new T2 hyperintense lesions within the cerebral white matter and subtle enhancement of the intraorbital portion of the left optic nerve after gadolinium administration.

Three weeks later, she developed bilateral internuclear ophthalmoplegia. T2-weighted cranial MR imaging showed a hyperintense lesion in the area of the medial longitudinal fascicle bilaterally within the pons. There continued to be multiple cerebral white matter lesions and signs of left optic neuritis (Fig 4). Intravenous methylprednisolone was once again instituted and within 6 weeks eye movements and vision returned to normal.

Discussion

Although brain stem involvement commonly occurs during the course of illness in patients with MS, isolated cranial nerve palsies are uncommon (8). Demyelinating lesions within the brain stem often result in double vision and a variety of ocular motility disturbances, including nystagmus, internuclear ophthalmoplegia, gaze palsies, and ocular motor cranial palsies. In a review of 1278 cases of cranial nerve III, cranial nerve IV, and cranial nerve VI paralysis, 40 cases of MS were identified (9). Cranial nerve VI is most commonly involved in combination with other signs of brain stem dysfunction (8, 10). Cranial nerve IV dysfunction in association with MS is infrequent (11). Combining three large retrospective studies investigating the causes of cranial nerve III paralysis, only 1.7% (16/889) of patients were noted to have MS (12–14). A review of the English-language literature identified seven case reports (five women and two men) describing MS and isolated cranial nerve III dysfunction (15–21). Clinical presentation varied in terms of the degree of ophthalmoplegia, ptosis, and pupil involvement. Three patients experienced associated eye pain or headache (16, 17, 19). MR imaging was obtained in five cases, with a discrete midbrain lesion identified in only three cases (18–20). No abnormalities of the peripheral cranial nerve III were seen in any of the five patients imaged.

Advancements in MR imaging technology have solidified its role as an important paraclinical test for establishing the diagnosis of MS and monitoring disease activity (22). It is an indispensable tool in the radiologic evaluation of cranial nerve dysfunction and in many cases can aid in determining the cause of cranial neuropathies (23). In particular, MR evaluation of cranial nerve III has been shown to be very effective (24). MR enhancement of the cisternal portion of cranial nerve III is always an abnormal finding

←

FIG 2. Axial fluid-attenuated inversion recovery (FLAIR) image (TR/TE, 9500/110) through the midbrain (*A*) demonstrates a subtle area of increased signal intensity (*arrows*) along the medial margin of the cerebral peduncle on the left side. No enhancement is seen on the axial gadolinium-enhanced T1-weighted image (600/17) (*B*) in this region. The coronal gadolinium-enhanced T1-weighted images (600/14) through the cisternal course of cranial nerve III (*C*) demonstrate subtle enhancement of the cranial nerve III on the left side (*arrows* in *C*). Notice the normal appearance of cranial nerve III on the right (*arrowheads* in *C*).

Third CN palsy and underlying lesions

Anatomic Site	3. CN Dysfunction Features	Associated Clinical Findings	Etiologies	Contrast Enhancement of 3.CN or Its Nuclei
Midbrain:				
Nuclear	(+/−) Bilateral pupil involvement	Supranuclear ocular motility deficits	Infectious:	
	(+/−) Bilateral ptosis		Lyme disease	Usually present
	Incomplete paresis (isolated extraocular muscle)		Syphilis	Variable
	Contralateral superior rectus muscle paresis		Inflammatory:	
			Multiple sclerosis	Variable
			Sarcoidosis	Present
			Autoimmune vasculitis	Variable
			Neoplastic:	
			Primary brain tumor	Variable
			Metastasis	Present
			Lymphoma	Present
			Traumatic	Usually none
			Vascular:	
			Ischemia	Variable
			Cavernous angioma	Usually none
			Arteriovenous malformation (AVM)	Enhancement of the AVM only
Fascicular	Complete or incomplete (divisional) paresis	Cerebellar Ataxia: Nothnagel's Contralateral dyskinesia: Benedickt's Contralateral hemiparesis: Weber's	Same as above	
	(+/−) Pupil involvement			
Subarachnoid space	Complete or incomplete (divisional) paresis	Multiple cranial neuropathies	Infectious:	
	(+/−) Pupil involvement	Meningeal irritation	Bacterial, viral or fungal meningitis	Present
		Mental status changes	Syphilis	Variable
		Raised intracranial pressure	Lyme disease	Usually present
			HIV	Usually present
			Inflammatory:	
			Multiple sclerosis	Variable
			Sarcoidosis	Present
			Inflammatory demyelinating polyneuropathy	Variable
			Neoplastic:	
			Lymphoma	Present
			Leukemia	Present
			Meningeal carcinomatosis	Present
			Schwannoma	Present
			Traumatic	Usually none
			Vascular:	
			Ischemia	Variable
			Aneurysm	Enhancement of the Aneurysm only
			Other:	
			Ophthalmoplegic migraine	Present
Cavernous sinus/ superior orbital fissure	Complete or incomplete (divisional) paresis	Multiple cranial neuropathies	Infectious:	
	(+/−) Pupil involvement	Visual Loss	Bacterial, viral or fungal meningitis	Present
		Proptosis	Syphilis	Variable
			Lyme disease	Usually present
			HIV	Usually present
			Inflammatory:	
			Tolosa-Hunt syndrome	Present
			Sarcoidosis	Present
			Neoplastic:	
			Lymphoma	Present
			Leukemia	Present
			Metastasis	Usually present
			Schwannoma	Present
			Pituitary macroadenoma	Present
			Cavernous sinus meningioma	Present
			Craniopharyngioma	Variable
			Traumatic	Usually none
			Vascular:	
			Ischemia	Variable
			Aneurysm	Enhancement of the aneurysm only
			Pituitary gland apoplexy	Usually none
			Other:	
			Ophthalmoplegic migraine	Present

and has been associated with intrinsic tumors of the nerve, infiltrative neoplasms, and inflammatory and infectious processes (Table) (25). The inflammatory demyelinating polyneuropathies have also been associated with enhancement of the ocular motor cranial nerves, including cranial nerve III (26). In addition, enhancement of cranial nerve III can be seen in patients with ophthalmoplegic migraine (27). Peripheral cranial nerve III enhancement has not been previously reported in association with MS, nor would it be expected, because the immunogenic target of MS is the CNS myelin or oligodendrocyte (28). Schwann cells are responsible for myelination of the cranial nerves from their exit from the brain stem. Surprisingly, in a study investigating the

incidence of cranial nerve V enhancement in MS, 2.2% (19/851) of patients were found to have enhancement of the distal portion of the nerve far from its exit site of the pons and beyond the anticipated transition zone between peripheral and central myelin (29). In a recent case series describing the radiologic evaluation of patients with cranial nerve VI paresis by using contrast-enhanced 3D MR imaging with multiplanar reconstruction, two cases of MS associated with enhancement of the cisternal portion of the nerve were identified (30).

It is difficult to attribute the MR enhancement of the cisternal portion of cranial nerve III in our case to a process other than MS. Despite the initial absence of cerebral lesions, later in the course of her disease our patient developed the typical white matter lesions of MS. Because MR was performed very early in the course of cranial nerve III palsy, the subtle abnormalities were not appreciated on the initial study (Fig 2). Because of the progressive nature of the pupil involving cranial nerve III, a cerebral angiogram was obtained to evaluate for the possibility of an aneurysm and arguably could have been avoided if the abnormal cranial nerve III enhancement was detected earlier and there was a higher clinical index of suspicion for a demyelinating process.

The demonstration of peripheral cranial nerve III enhancement in our patient supports the findings of other case reports and studies that MS can affect the PNS. Radiologic, pathologic, and electrophysiologic studies have documented PNS involvement in MS (4–7). Conversely, CNS involvement has been documented in patients with inflammatory demyelinating polyneuropathy (31). The association between MS and inflammatory demyelinating polyneuropathy is not clear, and a chance occurrence has been suggested but seems unlikely. A genetic predisposition and similarities between CNS and PNS myelin may explain the etioimmunopathogensis of PNS involvement in patients with MS (5, 7, 32). Whether PNS involvement in MS represents an underrecognized disease process, a variant of MS, or a distinct syndrome is not known at this time.

Conclusion

MR enhancement of the cisternal portion of cranial nerve III can be associated with MS. Increased clinical awareness and improved MR techniques may lead to a greater appreciation and detection of abnormal cranial nerve enhancement in MS patients with ophthalmoplegia due to ocular motor cranial nerve palsies.

References

1. Kalman B, Lublin FD. **Spectrum and classification of inflammatory demyelinating diseases of the central nervous system.** *Curr Neurol Neurosci Rep* 2001;1:249–256
2. Lucchinetti C, Bruck W, Noseworthy J **Multiple sclerosis: recent developments in neuropathology, pathogenesis, magnetic resonance imaging studies and treatment.** *Curr Opin Neurol* 2001;14:259–269
3. Wingerchuk DM, Lucchinetti CF, Noseworthy JH. **Multiple sclerosis: current pathophysiological concepts.** *Lab Invest* 2001;81:263–281
4. Poser CM. **The peripheral nervous system in multiple sclerosis: a review and pathogenetic hypothesis.** *J Neurol Sci* 1987;79:83–90
5. Waxman SG. **Peripheral nerve abnormalities in multiple sclerosis.** *Muscle Nerve* 1993;16:1–5
6. Pollock M, Calder C, Allpress S. **Peripheral nerve abnormality in multiple sclerosis.** *Ann Neurol* 1977;2:41–48
7. Rubin M, Karpati G, Carpenter S. **Combined central and peripheral myelinopathy.** *Neurology* 1987;37:1287–1290
8. Thomke F, Lensch E, Ringel K, Hopf HC. **Isolated cranial nerve palsies in multiple sclerosis.** *J Neurol Neurosurg Psychiatry* 1997;63:682–685
9. Richards BW, Jones FR Jr, Younge BR. **Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves.** *Am J Ophthalmol* 1992;113:489–496
10. Barr D, Kupersmith MJ, Turbin R, et al. **Isolated sixth nerve palsy: an uncommon presenting sign of multiple sclerosis.** *J Neurol* 2000; 247:701–704
11. Jacobson DM, Moster ML, Eggenberger ER, et al. **Isolated trochlear nerve palsy in patients with multiple sclerosis.** *Neurology* 1999;53:877–879
12. Rucker CW. **Paralysis of the third, fourth and sixth cranial nerves.** *Am J Ophthalmol* 1958;46:787–794
13. Rucker CW. **The causes of paralysis of the third, fourth and sixth cranial nerves.** *Am J Ophthalmol* 1966;61:1293–1298
14. Rush JA, Younge BR. **Paralysis of cranial nerves III, IV, and VI: cause and prognosis in 1,000 cases** *Arch Ophthalmol* 1981;99:76–79
15. Desai HB, MacFadyen DJ. **Multiple sclerosis presenting as third nerve palsy.** *Can J Neurol Sci* 1987;14:178–179
16. Uitti RJ, Rajput AH. **Multiple sclerosis presenting as isolated oculomotor nerve palsy.** *Can J Neurol Sci* 1986;13:270–272
17. Galer BS, Lipton RB, Weinstein S, et al. **Apoplectic headache and oculomotor nerve palsy: an unusual presentation of multiple sclerosis.** *Neurology* 1990;40:1465–1466
18. Ksiazek SM, Repka MX, Maguire A, et al. **Divisional oculomotor nerve paresis caused by intrinsic brainstem disease.** *Ann Neurol* 1989;26:714–718
19. Bentley PI, Kimber T, Schapira AH. **Painful third nerve palsy in MS.** *Neurology* 2002;58:1532
20. Lee AG, Tang RA, Wong GG, et al. **Isolated inferior rectus muscle palsy resulting from a nuclear third nerve lesion as the initial manifestation of multiple sclerosis.** *J Neuroophthalmol* 2000;20:246–247
21. Newman NJ, Lessell S. **Isolated pupil-sparing third-nerve palsy as the presenting sign of multiple sclerosis.** *Arch Neurol* 1990;47:817–818
22. Arnold DL, Matthews PM. **MRI in the diagnosis and management of multiple sclerosis.** *Neurology* 2002;58:S23–S31
23. Mark AS. **Oculomotor motion disorders: current imaging of cranial nerves 3, 4, and 6.** *Semin Ultrasound CT MR* 1998;19:240–256
24. Blake PY, Mark AS, Kattah J, Kolsky M. **MR of oculomotor nerve palsy.** *AJNR Am J Neuroradiol* 1995;16:1665–1672
25. Mark AS, Blake P, Atlas SW, et al. **Gd-DTPA enhancement of the cisternal portion of the oculomotor nerve on MR imaging.** *AJNR Am J Neuroradiol* 1992;13:1463–1470
26. Nagaoka U, Kato T, Kurita K, et al. **Cranial nerve enhancement on three-dimensional MRI in Miller Fisher syndrome.** *Neurology* 1996; 47:1601–1602
27. Mark AS, Casselman J, Brown D, et al. **Ophthalmoplegic migraine: reversible enhancement and thickening of the cisternal segment of the oculomotor nerve on contrast-enhanced MR images.** *AJNR Am J Neuroradiol* 1998;19:1887–1891
28. Rodriguez M, Lucchinetti CF. **Is apoptotic death of the oligodendrocyte a critical event in the pathogenesis of multiple sclerosis?** *Neurology* 1999;53:1615–1616
29. van der meijs MA, Tan IL, Barkhof F. **Incidence of enhancement of the trigeminal nerve on MRI in patients with multiple sclerosis.** *Mult Scler* 2002;8:64–67
30. Hosoya T, Adachi M, Yamaguchi K, et al. **Abducens nerve enhancement demonstrated by multiplanar reconstruction of contrast-enhanced three-dimensional MRI.** *Neuroradiology* 2001;43:295–301
31. Ormerod IE, Waddy HM, Kermode AG, et al. **Involvement of the central nervous system in chronic inflammatory demyelinating polyneuropathy: a clinical, electrophysiological and magnetic resonance imaging study.** *J Neurol Neurosurg Psychiatry* 1990;53:789–793
32. Berger T, Weerth S, Kojima K, et al. **Experimental autoimmune encephalomyelitis: the antigen specificity of T lymphocytes determines the topography of lesions in the central and peripheral nervous system.** *Lab Invest* 1997;76:355–364